



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference M0656/7046WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/19841	International filing date (day/month/year) 27/08/1999	Priority date (day/month/year) 27/08/1998	
International Patent Classification (IPC) or national classification and IPC C12N15/60			
Applicant MASSACHUSETTS INSTITUTE OF TECHNOLOGY			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input checked="" type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 21/03/2000		Date of completion of this report 20.10.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Roscoe, R Telephone No. +49 89 2399 2554 	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

The International Bureau of WIPO
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PCT

NOTIFICATION CONCERNING
DOCUMENTS TRANSMITTED

Date of mailing
(day/month/year)

20.10.2000

International application No: PCT/US99/19841

This International Preliminary Examining Authority transmits herewith the following documents:

1. ☐ demand (Rule 61.1(a)).
2. ☒ copy of the international preliminary examination report and its annexes (Rule 71.1).
3. ☐ _____ other documents (*specify*):

Name und mailing address of the IPEA/

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International application No. PCT/US99/19841

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-77 as originally filed

Claims, No.:

1-57 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
 - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

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Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 22-29, 30(part), 32, (33-45)(part).

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 22-29, 30(part), 32, (33-45)(part).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.

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- ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:
- see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-21, 30(part), 31, (33-45)(part), 46-57 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 7, 14, 15, 18, 19, 33-45(part), 48-51, 53, 54
	No:	Claims	1-5, 8-13, 16, 17, 20, 21, 30, 31, 46, 47, 52, 55-57
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21, 30, 31, 33-45, 46-57
Industrial applicability (IA)	Yes:	Claims	1-21, 33, 34, 45, 48, 51-57
	No:	Claims	30-32, 35-44, 46, 47, 49 and 50

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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I. Basis

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

Sequence listing pages 1-8 are also included in the basis of the present assessment.

II. Priority

The entire subject-matter of the present application appears to be entitled to priority from US application number 60/098153 (08.10.99). Hence, document D4 is not relevant prior art.

III. No Opinion

No opinion can be given for those claims for which no International Search Report has been established (i.e. claims 22-29, 30(part), 32, (33-45)(part)).

IV. Lack of Unity

The present application comprises 2 invention groups as set out in the International Search Report. Preliminary Examination can only be carried out on invention group I - modified heparinase II and matter relating thereto (claims 1-21, 30(part), 31, (33-45)(part), 46-57).

Invention group I is further considered intrinsically non-unitary. Mutants of the kind claimed by applicant are specified in the prior art. Hence, no common inventive concept would appear to link the claimed mutants. Applicant will have to eventually limit himself to a specific mutant. However, for practical reasons, this matter shall not be addressed in the International Phase.

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

Novelty (Art.33(2) PCT)

D2 is the closest prior art. D2 discloses various Heparinase II mutants in which cysteine residues have been modified. Modifications of individual histidine residues at one of positions 48, 238, , 249, 252, 347, 440, 473, 579, 682, to alanine were tested. Several mutants were void of enzymatic activity to either heparin or heparin sulphate (238, 406, 408, 451, 579). Mutants 252, 347 and 440, however, displayed differential activity towards heparin or heparin sulphate. The H347A mutant showed a marked decrease in activity (suggested to be due to proximity to cysteine 348). H440A has a reduced activity towards heparin. Precise quantitative data relating to the activity of the different mutants is not given. The document does not suggest medical applications yet suggests that mutants may be useful in developing heparinase II as a biological tool.

Until proven otherwise by the applicant, D2 is cited as novelty-destroying against the following claims (applicant is also referred to section on clarity): 1-5, 8-13, 16, 17, 20, 21, 30, 31, 46, 47, 52, 55-57. Indeed certain of these claims specifically refer to products already disclosed in D2 (claims 13, 16, 17, 31, 52).

D1 discloses the sequence of Heparinase II and recombinant expression thereof (example 7). No mutants with modified activities are disclosed. Hence, D1 does not anticipate any of the present claims.

Inventive Step (Art.33(3) PCT)

With regard to uses of Heparinases (including potential medical uses), it is noted that given the knowledge of the possible role of hesparinases and their substrates in various disease states (see for example introduction of D1), and further in view of the fact that applicant has not been adding to the medical knowledge in the field, claims to medical uses of heparinase mutants could only be considered inventive where the mutants are inventive per se. The same applies to trivial matter such as pharmaceutical compositions or immobilized enzymes.

Claims 14, 15 and 49 relate specifically to C348 mutants. D2 already implicates this position as a potential active site residue (p.10166, col.2). Hence, mutants at

this position would be obvious to make for the purpose of testing whether the implication is correct.

Since no inventive mutants are identified, inventive step is not acknowledged for any of the claims.

Industrial Applicability (Art.33(4) PCT)

For the assessment of the present claims 30-32, 35-44, 46, 47, 49 and 50 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 30-32, 35-44, 46, 47, 49 and 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VIII. Certain observations

Clarity (Art.6 PCT)

The term "product profile" is considered technically unclear.

The majority of the claims can be considered unclear since they relate to modified enzyme defined by the result to be achieved. Obtaining an enzyme with a somehow modified substrate specificity / reaction rate is the problem which applicant addresses with the claimed subject-matter. The claims need to specify the solution to the problem i.e. how the problem was overcome (in this case by introducing specific mutations). Further, claims need to clearly distinguish the claimed subject-matter from the prior art. In the present case, it is unclear which

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of applicants mutations and which in the prior art (which overlaps substantially) can be considered to meet the specified "product profile" alterations. Novelty cannot be acknowledged for any of the claims where this is unclear. Indeed, given that applicants mutants were mainly known in the prior art and that it is to be assumed that the claims are drafted according to the types of effect achieved by these mutants, it would appear very likely that a substantial number of the claims are anticipated by the mutants already disclosed in D2.